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The efficacy of aerobic training in improving the inflammatory component of asthmatic children. Randomized trial

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Asthma;
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Summary
Few studies have been conducted on the effects of aerobic exercise in children with asthma, particularly on the inflammatory component and functional outcomes. This study evaluated the effect of aerobic exercise on inflammation, functional capacity, respiratory muscle strength, quality of life and symptoms scores in asthmatic children.

This was a 6-week randomized trial (NCT0192052) of 33 moderately asthmatic children (6—17 years).

Patients were randomized aerobic training (exercise group; $n = 14$), while another group did not exercise (control; $n = 19$). Primary endpoint was evaluations serum cytokines (IL-17, IFN, TNF, IL-10, IL-6, IL-4 and IL-2) assessed by flow cytometry. The six-minute walk test, pulmonary function, quality of life and symptoms (asthma-free days) were secondary endpoint. The Mann—Whitney test was used to evaluate the independent variables and the Wilcoxon test for paired variables. The *t*-test was used for the remaining calculations. Significance was determined at 5%.

Aerobic training failed to modify the inflammatory component. In the exercise group, an increase occurred in functional capacity ($p < 0.01$) and peak expiratory flow ($p = 0.002$), and maximal inspiratory ($p = 0.005$) and expiratory pressure ($p < 0.01$) improved. Furthermore, there was a significant increase in all the domains of the PAQLQ. The children who exercised had more asthma-free days than the controls ($p = 0.012$) and less sensation of dyspnea at the end of the study ($p < 0.01$).

In conclusion, six weeks of aerobic exercise no changes in plasma cytokine patterns in asthmatic children and adolescents; however, an improvement was found in functional capacity, maximal respiratory pressure, quality of life and asthma-related symptoms.

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Introduction

Practicing physical activity regularly is known to be an important component of a healthy lifestyle and should be a routine part of children's lives, since exercise positively affects their psychosocial and motor development and their self-image [1]. Low levels of physical activity lead to chronic deconditioning, therefore, it is not surprising that children with asthma, particularly more severe forms of asthma, are less active and often have lower cardiorespiratory fitness compared to healthy children of the same age [1,2]. Asthma symptoms may introduce some limitations to routine activities, tending to make sufferers more sedentary and inclining them towards avoiding physical activity [1—3].

There has been a general reduction in physical activity levels in adults and children over the past three decades, resulting in an increase in the incidence of sedentariness worldwide [1,4,5]. However, different studies have dealt with this subject in different ways, with significant variations in methodology, in the ways in which physical activity is quantified, in the severity of the disease and even in conflicting reports made by the children's families [1,6].

Physical exercise improves cardiopulmonary fitness and asthma-related symptoms, reduces the number of visits to the emergency room and the frequency of exacerbations, and improves patients' quality of life, as well as certain psychosocial aspects in these individuals [6—10]. It remains unclear, however, whether the benefits of exercise observed in asthmatics are the result of a direct effect in improving inflammation in the airways or whether they are a consequence of better cardiorespiratory fitness and peripheral muscle strength or both [9,11].

A systematic review showed the effects of physical training in an animal model with atopic asthma, in which a reduction in Th2-lymphocyte cytokine levels and an increase in Th1 and regulatory T-cell (Treg) response have already been shown [12]. Only two studies have evaluated the effects of aerobic exercise on inflammation in asthmatic patients [9,11]. One reported a reduction in the serum levels of immunoglobulin E [9], while the other found a reduction in eosinophil count in sputum [11].

Few studies have shown the effects of aerobic exercise training in children with moderate and severe asthma. A search of the PubMed database for the 2000—2013 period using the key words *aerobic exercise*, *physical training*, *child* and *asthma* revealed only three studies [9,10,13] on the subject. Those studies showed an improvement in physical capacity but varying results on quality of life. An improvement in symptoms score was found in only one study [13] and an improvement in inflammation in another [9].

The principal objective of the present study was to evaluate the short-term efficacy of an aerobic physical training program on inflammatory response in asthmatic children. A secondary objective was to evaluate the effects of the intervention on functional capacity, respiratory muscle strength, quality of life and the number of asthma-free days.

Method

Patient selection criteria

Children and adolescents of 6—17 years of age with persistent moderate asthma, controlled by low or moderate doses of an inhaled corticosteroid for at least six months, were selected for the study. The participants were selected from children consulting a pediatric pneumologist between March 2012 and April 2013 at a specialist clinic for respiratory diseases.

The study selection criteria took into consideration the classification defined by the Global Initiative for Asthma [14], **forced expiratory volume** in 1 s (FEV_1) below 80% of the predicted value and absence of any exacerbation or change in medication in the preceding 30 days. Patients with cardiovascular disease, lung disease or any musculoskeletal disorder that could hamper evaluation or the performance of physical activity were excluded.

The study was approved on October 20, 2010 by the internal review board of the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP) under reference number 1900. In all cases, the child's parent or guardian signed an informed consent form.

Study design

A randomized clinical trial was conducted in accordance with the CONSORT statement [15]

Participants were allocated to a control group ($n = 19$) or to the exercise group ($n = 14$) in accordance with a table of sequential random numbers drawn up using the Epi-Info software program, version 6.04 b. Randomization was conducted by a professional who was not involved in evaluating or analyzing the data. Since this was an intervention that involved performing physical exercise, blinding was not an option. The allocation list was only opened after the groups were formed. At the time of randomization, each participant was given a sealed, opaque envelope by a professional who did not otherwise participate in the study.

Training program

The intervention consisted of supervised aerobic training performed three times a week for six weeks on an electric treadmill (Pro-Form®, model 325i, São Paulo, Brazil) in an appropriate environment at a temperature of 22—25 °C, with the participants dressed in sports shorts and wearing running shoes. The exercise consisted of a 5-min stretching period focused on the major muscle groups of the lower limbs, followed by 10-min of warm-up, 20-min of training in the first and second weeks and 30-min in the third to sixth weeks, followed by a 5-min cooling down period. The warm-up and cooling down periods consisted of gentle walking on the treadmill, with heart rate maintained at 40%—50% of maximum heart rate.

During exercise, intensity was controlled by maintaining heart rate between 70% and 80% of maximum heart rate, with reference values calculated according to the Karvonen formula [16].

The modified Borg scale, heart rate, respiratory rate and blood oxygen saturation (SpO_2) were evaluated prior to and immediately following each exercise session.

If necessary, the participants were instructed to use β2 agonists prior to or during the exercise session. To assure compliance, the participants were given public transportation tickets to enable them to participate in the program, and telephone contact was also maintained. The participants in the control group were instructed to continue with their usual routine of physical activity.

Determination of inflammatory mediators

To obtain the primary outcome (inflammation), the collection of peripheral blood (4 ml) was performed in tubes containing EDTA anticoagulant by a skilled lab professional. Afterwards, a centrifugation was performed in order to remove plasma and to separate the cellular components of peripheral blood into Ficoll-Hypaque gradient (GE Healthcare Bio-Sciences®), which were subsequently frozen at −80 °C. Plasma samples and the test for detection of cytokines were analyzed in the molecular biology laboratory of the Institute.

The following plasma cytokines were measured: Th1/Th2/Th17 (IL-2, IL-4, IL-6, IL-10, IFNγ, TNF, IL-17A) by flow cytometry using a cytometric bead array (CBA) kit for cytokines Th1/Th2/Th17 (BD Biosciences®, San Jose, CA, USA) in a FACSCalibur flow cytometer (BD Biosciences®, San Jose, CA, USA) according to the manufacturer's instructions. A total of 2100 events were analyzed using the FCAP Array program, version 3.0 (BD Biosciences®, San Jose, CA, USA). The analysis of the samples occurred at the end of the training time for all participants.

The lower limits of detection for the cytokines in pg/mL were: IL-2 = 4.9, IL-6 = 2.4, IL-10 = 4.5, TNF = 3.8, IFN = 3.7 and IL-17A = 18.9.

Baseline evaluation and follow-up

A score of Habitual Level Physical Activity was elaborated and applied to both groups at admission [17]. In accordance with their weekly frequency of physical activity, the participants were classified as sedentary (no physical activity), practising some physical activity ($\leq$2 h/week) or active (practicing $>$2 h of physical activity per week or participating in formal sporting activities).

The following evaluations were performed in both groups at the beginning of the study and at the end of the sixth week: (i) The 6-min walk test (6MWT), as standardized by the American Thoracic Society [18]. (ii) Respiratory muscle strength, using a mechanical pressure gauge (Comercial Médica®, São Paulo, Brazil). (iii) A pulmonary function test was performed using a digital spirometer (One Flow, Clement Clarke International, UK) in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society (ATS/ERS) [19] in which forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio and peak expiratory flow (PEF) were assessed. The values obtained were expressed as percentages of the predicted normal value, in accordance with the ATS criteria [20]. (iv) The occurrence of symptoms and the use of any medication were recorded in a diary adapted from that used by Mendes et al. [21] and filled out by the patient's parent or guardian. (v) Quality of life was determined using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) [22].

Criteria defining discontinuation and loss to follow-up

Participants were discontinued from the study if they experienced exacerbations on three or more occasions, if they had a severe crisis or if they had to be hospitalized because of the disease. Participants who failed to attend one of the evaluations or who missed more than 25% of the exercise sessions (4 sessions) were considered lost to follow-up.

The co-interventions were decided according to the attending pediatric pneumologist and were based on the definitions drawn up by the Global Initiative for Asthma (GINA) [14]. The investigators did not interfere with any part of the treatment other than the proposed intervention.

Statistical analysis

Within the time established to conduct this study, it was only possible to include 33 patients. No data were found in the literature to enable sample size to be calculated based on the primary objective.

Frequency distributions were obtained for all the variables and descriptive analysis was carried out (means or medians), and 95% confidence intervals were calculated. The continuous variables were assessed using the Kolmogorov—Smirnov test for normality, and those with a normal distribution were then compared using the *t*-test. Analysis of the cytokines showed non-normal distribution; therefore, the Mann—Whitney test for independent variables was applied, with the Wilcoxon test being used for paired values.

The software used was the STATA statistical software program, version 12.1SE. Significance level was defined as 5%. All analyses were conducted using the intention-to-treat approach.

Results

There were no statistically significant differences between the exercise and control groups at baseline, as shown in Table 1. The majority of the children evaluated had persistent moderate asthma. Most had normal weight and a sedentary lifestyle and used low or moderate doses of inhaled corticosteroids in combination with long-acting β2-agonists. The flowchart showing the enrollment and follow-up of the participants in the study is shown in Fig. 1.

All the children managed to keep up with the intensity of the exercise sessions without suffering exacerbations. There were no changes in medication during the program. No detectable intra-group or inter-group differences were found in plasma cytokine levels (Table 2).

No changes occurred in spirometric values following aerobic training, with the exception of peak expiratory flow

(PEF), which was higher in the group submitted to exercise ($p = 0.002$). Respiratory muscle strength increased significantly only in the exercise group, in which increases were found in maximum inspiratory pressure ($p = 0.005$) and in maximum expiratory pressure ($p = 0.01$) (Table 3).

The distance covered in the 6MWT increased by a mean of 99.7 m between baseline and the end of the study in the exercise group ($p < 0.01$), but remained unchanged in the control group ($p = 0.977$). There were no statistically significant differences between the groups (Table 3).

Overall PAQLQ score and the score for each domain alone (symptoms, activity limitation and emotional function) increased significantly in the exercise group. Furthermore, the score in this group improved compared to that of the controls (Table 4).

In the evaluation of the symptom scores, the mean number of asthma-free days was greater in the exercise group than in the control group (29.8 $\pm$ 6.6 days versus 20.7 $\pm$ 9.3 days; $p = 0.012$). At the end of the study, the sensation of dyspnea was lower in the exercise group compared to the control group (0.7 $\pm$ 0.3 versus 3.2 $\pm$ 0.3; $p < 0.01$).

Discussion

The results of the present study showed that following a 6-week program of aerobic exercise no changes could be found in plasma cytokine patterns in asthmatic children and adolescents. However, there was an improvement in functional capacity, in maximal respiratory pressure, quality of life and in the number of asthma-free days.

These results may be justified by the fact that detection of cytokine levels in plasma was limited by the system that was available for use, which has cut-off limits above the values obtained. Furthermore, it is possible that the sample size may have been too small for any statistically significant difference to be detected between the groups. Likewise, Doe et al. [23] failed to find any changes in IL-17 levels in the sputum of asthmatic patients and patients with chronic obstructive pulmonary disease (COPD). Another possible explanation for the finding may be the low rate of physical activity in this population and/or the relatively short period of the intervention; however, there is no clear evidence that the program used was insufficient in this respect. On the other hand, the American Academy of Pediatrics recommends that every adolescent has at least an hour of exercise per day [24].

Aerobic exercise performed for 12 weeks by 68 adults with moderate or severe persistent asthma resulted in a reduction in eosinophils in sputum [11]. A study in which children performed 50-min of aerobic exercise twice a week for 12 weeks showed a reduction in total and specific IgE levels in relation to the controls, with no differences in the number of eosinophils [9]. It should be noted that this was the first study to evaluate plasma cytokines using flow

Table 1 Baseline characteristics of the study sample.

Variables	Group		p-Value
	Control ($n = 17$)	Exercise ($n = 10$)	
Sex, n (%)			
Male	9 (52.9)	6 (60.0)	1.000
Female	8 (47.1)	4 (40.0)	
Type of asthma, n (%)			
Moderate	16 (94.1)	9 (90.0)	1.000
Severe	1 (05.9)	1 (10.0)	
FEV_1 (l)	1.81 $\pm$ 0.58	1.96 $\pm$ 0.62	0.546
FEV_1 (%)	82.3 $\pm$ 13.2	85.6 $\pm$ 22.4	0.583
Therapy in use, n (%)			
Low/moderate dose of inhaled corticosteroid	6 (35.3)	2 (20.0)	0.836
Low/moderate dose of inhaled corticosteroid + long-acting β2-agonist	10 (58.8)	7 (70.0)	
High dose of inhaled corticosteroid + long-acting β2-agonist	1 (5.9)	1 (10.0)	
Physical activity level at baseline, n (%)			
Sedentary lifestyle	12 (70.6)	6 (60.0)	0.789
Regular physical activity (>2 h/week)	4 (23.5)	4 (40.0)	
Sports activities (>3 h/week)	1 (5.9)	0 (0.0)	
Body weight n (%)			
Underweight	0 (0.0)	1 (10.0)	0.397
Normal weight	12 (70.6)	5 (50.0)	
Overweight	2 (11.8)	3 (30.0)	
Obesity	3 (17.6)	1 (10.0)	
Age, mean $\pm$ SD	11.4 $\pm$ 2.3	11.7 $\pm$ 2.3	0.704
Weight, mean $\pm$ SD	40.6 $\pm$ 13.1	45.2 $\pm$ 12.1	0.368
Body mass index, mean $\pm$ SD	18.7 $\pm$ 3.9	20.9 $\pm$ 6.1	0.256

t-test, $p < 0.05$.

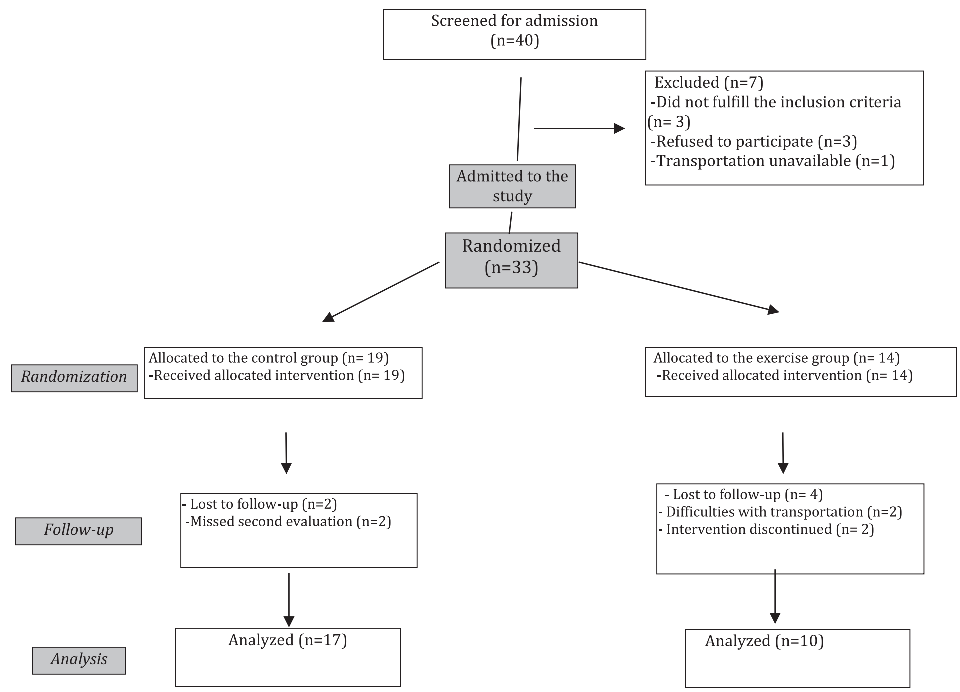

Figure 1 Flowchart of the admission of participants to the study and their follow-up.

cytometry following an aerobic exercise program in children; therefore, comparison with other studies is difficult.

Although there was no improvement in the inflammatory markers, aerobic training resulted in an improvement in functional capacity, maximal respiratory pressure, quality of life and in the number of asthma-free days.

An increase was found in the absolute values of PEF in the exercise group in the present study. In agreement with these results, the study conducted by Basaran et al. was the only one to report an improvement in PEF following eight weeks of exercise training performed three times weekly [13].

Table 2 Comparison of intra-group and inter-group mean plasma cytokine measurements prior to commencement of the aerobic training program and after the end of the program in asthmatic children.

Variable	Group	*n*	Baseline		Final	
			Median	(IQR: P25:75)	Median	(IQR: P25–P75)
IL-17	Control (*C*)	13	17.1	11.5–63.4	17.1	10.9–49.4
	Exercise (*E*)	9	23.6	8.2–32.4	28.4	6.7–67.4
	C vs. *E*: *p*-value*			0.920		0.483
IFN	Control (*C*)	13	0.0	0–0	0.0	0–14.9
	Exercise (*E*)	9	0.0	0–0	0.0	0–8.6
	C vs. *E*: *p*-value*			0.843		0.777
TNF	Control (*C*)	13	0.0	0–21	0.0	0–6.2
	Exercise (*E*)	9	2.2	0–8.2	5.3	0–6.5
	C vs. *E*: *p*-value*			0.971		0.326
IL-10	Control (*C*)	13	0.0	0–8	4.1	2.1–9.7
	Exercise (*E*)	9	0.0	0–3.9	5.4	0–13
	C vs. *E*: *p*-value*			0.635		0.910
IL-6	Control (*C*)	13	0.0	0–9.7	0.0	0–2.4
	Exercise (*E*)	9	0.0	0–0	0.0	0–0
	C vs. *E*: *p*-value*			0.256		0.734
IL-4	Control (*C*)	13	5.2	0–21.3	0.0	0–6.1
	Exercise (*E*)	9	0.0	0–9.1	9.1	3.7–13.6
	C vs. *E*: *p*-value*			0.488		0.057
IL-2	Control (*C*)	13	4.9	0–24.3	4.1	3.2–8.5
	Exercise (*E*)	9	6.0	0–11.2	8.8	0–4.6
	C vs. *E*: *p*-value*			0.811		0.418

IL-interleukin, IFN-interferon, TNF-tumor necrosis factor. *Mann–Whitney test for independent samples (inter-groups), $p < 0.05$.

Table 3 Inter- and intra-group comparison of the variables related to pulmonary function and the distance covered in the 6-min walk test between the exercise and the control groups prior to commencement of the aerobic training program and after the end of the program in asthmatic children.

Variable	Group	*n*	Baseline	Final	*p*-Value
			Mean (SD)	Mean (SD)	
VEF_1, % Predicted	Control (*C*)	17	2.2(0.2)	2.2(0.1)	0.728
	Exercise (*E*)	10	2.3(0.2)	2.2(0.2)	0.383
	C vs. *E*: *p*-value		0.563	0.925	
FVC, % Predicted	Control (*C*)	17	2.5(0.2)	2.5(0.2)	0.087
	Exercise (*E*)	10	2.7(0.2)	2.7(0.2)	0.665
	C vs. *E*: *p*-value		0.305	0.352	
FEV_1/FVC, % Predicted	Control (*C*)	17	0.9(0.0)	0.9(0.0)	0.245
	Exercise (*E*)	10	0.9(0.0)	0.9(0.0)	0.312
	C vs. *E*: *p*-value		0.932	0.088	
PEF, l/min	Control (*C*)	17	215.9(16.7)	195.3(12.7)	0.135
	Exercise (*E*)	10	226.5(21.8)	261.0(16.6)	0.054
	C vs. *E*: *p*-value		0.699	0.002	
Pimax, cmH_2O	Control (*C*)	17	78.2(5.1)	80.6(4.9)	0.499
	Exercise (*E*)	10	81.0(6.6)	103.6(6.4)	<0.001
	C vs. *E*: *p*-value		0.739	0.005	
Pemax, cmH_2O	Control (*C*)	17	70.0(4.3)	70.8(3.9)	0.762
	Exercise (*E*)	10	83.0(5.6)	104.0(5.0)	<0.001
	C vs. *E*: *p*-value		0.065	<0.001	
Distance, Meters	Control (*C*)	17	425.3(29.2)	425.6(28.8)	0.977
	Exercise (*E*)	10	413.6(38.0)	513.3(37.5)	<0.001
	C vs. *E*: *p*-value		0.807	0.064	

FEV_1 (Forced expiratory volume in 1 s), FVC (forced vital capacity), PEF (peak expiratory flow), Pimax (maximum inspiratory pressure), Pemax (maximum expiratory pressure), Distance (distance covered by the patient in the 6-min walk test). *t*-test, $p < 0.05$.

Table 4 Inter- and intra-group comparison of the variables for the quality of life questionnaire (PAQLQ) prior to commencement of the aerobic training program and after the end of the program in asthmatic children.

Variable	Group	*n*	Baseline	Final	*p*-Value
			Mean (SD)	Mean (SD)	
Activity limitation	Control (*C*)	17	5.2(0.3)	5.2(0.3)	0.933
	Exercise (*E*)	10	4.8(0.4)	6.3(0.4)	<0.001
	C vs. *E*: *p*-value		0.380	0.033	
Emotional function	Control (*C*)	17	5.3(0.3)	5.2(0.3)	0.848
	Exercise (*E*)	10	4.8(0.4)	6.2(0.4)	<0.001
	C vs. *E*: *p*-value		0.293	0.046	
Symptoms	Control (*C*)	17	5.1(0.3)	5.0(0.3)	0.377
	Exercise (*E*)	10	5.1(0.3)	6.1(0.4)	<0.001
	C vs. *E*: *p*-value		0.932	0.019	
Total score	Control (*C*)	17	5.2(0.2)	5.1(0.3)	0.642
	Exercise (*E*)	10	5.0(0.3)	6.2(0.4)	<0.001
	C vs. *E*: *p*-value		0.528	0.031	

t-test, $p < 0.05$.

Particularly in obstructive diseases, hyperinflated lungs decrease the mechanical advantage of the diaphragm by reducing its curvature, and impair the capacity of other respiratory muscles to generate force [25]. A previous study showed that the variation in maximum inspiratory pressure reflects the structural adaptation of the inspiratory muscles, and that adults with asthma have a reduction of up to 30% in maximal respiratory pressures [26]. In the present study, significant gains in maximum inspiratory and expiratory pressures were found in the exercise group, probably as the result of adaptation to the physical effort generated during the training period. To the best of our knowledge, no studies have been conducted in which respiratory pressure was evaluated in asthmatic children following physical training.

A systematic review including data from 16 studies involving 516 asthmatic children reported that physical training improved cardiopulmonary fitness [27]. In the present study, a significant gain was found in functional capacity in the exercise group alone, as shown by an increase in the distance covered in the 6-min walk test; however, although borderline, this difference was not statistically significant. Nevertheless, it has yet to be confirmed which type of program is better (time or intensity) insofar as achieving more expressive gains in physical fitness is concerned [28]. A 6-week intervention period may have been too short to achieve more expressive results. Furthermore, there are no definite data in the pediatric population with respect to a minimum distance that would be clinically significant. The results of the present study showed a mean difference in the distance covered in the 6MWT of 87.7 m between the exercise group and the control group; however, it is unclear whether this gain is clinically relevant. A previous study conducted with asthmatic children reported an increase of 26 m in the group submitted to regular physical training [13].

Few studies have focused on health-related quality of life in asthmatic children submitted to aerobic exercise programs and those that did so reported conflicting results [9,10,13]. The present study found a significant increase in all the items in the questionnaire, in addition to a better overall PAQLQ score in the exercise group, which may be explained by the fact that 60–70% of the children were sedentary and failed to practice any type of physical activity prior to the study. The beneficial effects of an increase in exercise capacity are also reflected in psychological gains and improved self-esteem, which may have positively affected health-related quality of life [5,29].

The improvement in asthma symptoms found in the present study, as shown by the increase in the number of asthma-free days, is in agreement with the findings of Mendes et al. [21], who also reported this outcome in adults following an aerobic training program.

A wide variation was found between studies in relation to the duration and frequency of exercise, as well as the programs applied. In those studies, the frequency of exercise ranges from a minimum of twice a week to a maximum of six times a week, while the duration of exercise ranges from a minimum of 10-min to a maximum of 2 h. Regarding the duration of the intervention, studies have reported variations that range from a minimum of four weeks to a maximum of two years [5,29].

The small sample size was the greatest limitation of this study. Another issue was that the method used for measuring cytokines in plasma, despite the fact that no previous studies have been published on this subject, was incapable of detecting the actual behavior of these profiles.

Despite the fact that physical activity is not specifically recommended in children with moderate and severe asthma, the benefits of careful, individualized physical training suggest that it should be encouraged, since, when the disease is under control, improvements are found in important endpoints such as functional capacity, maximal respiratory pressure, quality of life and disease-related symptoms.

Six weeks of aerobic exercise resulted in no changes in plasma cytokines; however, increases were found in functional capacity, maximal respiratory pressure, quality of life and disease-related symptoms in asthmatic children. Additional studies should be conducted using more appropriate methodology for measuring inflammatory markers at tissue level to further evaluate the effect of physical training on the inflammatory component of the disease.

Conflicts of interest

None declared.

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